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PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	PETRA BOYLE GAYLE D. WETZEL KENNETH J. LEMBACH	DECLARATION UNDER 37 C.F.R. § 1.132
Serial No.:	08/026,957	EXAMINER: R. D. BUDENS
Filed:	March 5, 1993	ART UNIT: 1806
For:	HUMAN ANTI-TNF ANTIBODIES	

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Gayle D. Wetzel, declare as follows:

1. I have been awarded a Ph.D. degree in microbiology from the University of Texas and have approximately 10 years working experience with monoclonal antibodies. I am a co-inventor in the above-entitled Patent Application.

2. To support a rejection under 35 USC 112 (non-enablement for scope of claims), the Examiner stated that it is not clear whether suitable lymphocytes could be obtained from other CMV infected individuals or other individuals having anti-TNF autoantibodies. In citing Applicants' statements at page 11, lines 4 - 14 and page

37, lines 6 - 7, the Examiner stated (page 5, lines 15 - 16) that the Applicants' required a CMV positive donor. This is not correct. It is not stated that such a donor is required, on page 11. Although the donor for the B5 hybridoma happened to be CMV seropositive, several other IgM anti-TNF monoclonal antibodies were generated from several different donors, some of whom were CMV seropositive and others whose CMV status is unknown.

3. Regarding the Examiner's comments in the paragraph bridging pages 4 and 5, it should be noted that the B5 monoclonal antibody of the examples was expressed by lymphocytes from a single individual who had been, at one time, infected with CMV and, therefore, had antibodies to CMV in his/her blood. However, the other anti-TNF monoclonal antibodies listed in Table 1 of the Patent Application, and the F448-1D1-A8 anti-TNF monoclonal antibody deposited with the ATCC (and referred to in Figure 8) were derived from 5 different individuals. Of the 5 different donors, 2 were known to be CMV seropositive and the CMV status of the other 3 was unknown. The A1 and B5 antibodies came from one CMV positive donor. The F12 and D6 came from a different CMV positive donor. The B6, F6, G7 and C1 IgM and D8 and F10 IgM antibodies listed in Table 1 came from a fourth donor of unknown CMV status. The A8 antibody, referred to in Figure 8, came from a fifth donor of unknown CMV status.

The multiple anti-TNF monoclonal antibodies derived from several different donors are important for several reasons. First, given the examples of the Specification, a person skilled in the art of making human hybridomas and monoclonal antibodies would be able to reproduce the results without undue experimentation. Second, the probability of obtaining monoclonal antibodies similar to B5 is not

low, as suggested by the Examiner's comments on page 5, lines 12 - 16.

4. The Examiner addresses the "starting material" describing it as "a CMV-infected human lymphocyte donor having autoantibodies to human TNFα." There appears to be a misunderstanding by the Examiner in this description. The human donors, to our knowledge, were not infected with CMV at the time they donated peripheral blood. The fact that their sera contained antibodies to CMV, merely indicates that they had been infected with CMV at some time in the past. About 90% of the adult population in the United States is seropositive for antibodies to CMV. Hence, although it does not appear to be necessary to have a CMV positive donor to duplicate the present invention, obtaining such a donor should not involve undue effort. Since I have no reason to believe that one CMV seropositive donor is substantially different from another in the ability of its lymphocytes to generate monoclonal antibodies to TNF, obtaining lymphocytes from a donor similar to those used should yield monoclonal antibodies to TNF similar to those generated in the Specification without involving undue experimentation.

5. The Examiner's statement on page 5 that the donors have "autoantibodies to human TNFα" is inaccurate. There is no evidence in the Specification that the donors had autoantibodies to TNF. In the Application, there is no statement or implication, nor was there any intention or implication, that having autoantibodies to human TNFα is necessary or, in any way, was responsible for the generation of monoclonal anti-TNF antibodies from the lymphocytes of a given donor. As far as is known, the autoantibody status of an individual has no correlation to the ability of the individual's

lymphocytes to be stimulated to make anti-TNF monoclonal antibodies under the conditions described in the Application.

6. The fact that the Applicants on page 37, lines 6 - 7 question the significance of the CMV seropositive status of the donors was intended to be a gratuitous statement. There was no reason to suspect that CMV seropositivity is related, in any way, to the ability to generate anti-TNF monoclonal antibodies from a donor's lymphocytes. The statement on page 37 was made to be perfectly open and honest in our ignorance in this matter and in the general interest in disseminating information in a scientific manner. In making this statement, the Applicants suspected there is no difference and we have no reason to believe there would be a difference, but we have not examined the issue scientifically. As pointed out above, since over 90% of the U.S. population is CMV seropositive, the source of the lymphocytes should have no bearing on the reproduceability of our invention.

7. The Examiner's reliance on "well known unpredictability" in making monoclonal antibodies and the "low probability of obtaining the same or similar monoclonal antibodies to a particular antigen" is misplaced. Making hybridomas is not unpredictable. One may have a somewhat low probability of obtaining exactly the same monoclonal antibody. However, it is not true that obtaining qualitatively similar antibodies is low, since the sequence of two different antibodies may vary subtly while no apparent difference in their affinities or specificities can be observed. In fact, it is quite common to obtain several different antibodies which are similar in their binding to antigen properties.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States code and that such willful false statements may jeopardize the validity of the Application or any patents issuing thereon.

1/21/94
Date

Gayle D. Wetzel, Ph.D.